the claims as originally filed. Claims 37-39 have been added. Support for these claims is found, for example, at page 5, lines 16-17, and in Figures 1A and 2G. No new matter has been added.

Claims 19-30 and 33-36 have been withdrawn by the Examiner.

Claims 1, 3-9, 11-17, 31-32, and 37-39 are currently under examination.

Applicants note with appreciation that the Examiner considers that Claims 1-8, 10-18 and 31-32 are "free of the art of record", and that "Claim 18 would be found allowable if rewritten in independent form encompassing all limitations of the independent claims and any intervening claims."

Information Disclosure Statement

Pursuant to a telephone conversation between the Attorney and the Examiner, copies of the IDS and Supplemental IDS forms were sent by facsimile to the Examiner on March 11, 2002. A copy of this facsimile, including the transmission receipt, is enclosed as Exhibit A. Applicant's Attorney had understood from the conversation that the Examiner had requested only the 1449 forms, and not the references themselves; it thus appears that there was a miscommunication with the Examiner, who stated in the Office Action that he believed the references would be sent as well. The IDS is resubmitted herein, together with the references. These documents were previously filed on May 23, 2001 and received in the U.S. PTO on May 29, 2001 as shown by the postcard receipt, a copy of which is enclosed as Exhibit B.

Specification

The Examiner rightfully noted that the species of ATG $(GCG)_{6+n}$ GCA, wherein n=3 was not represented in the sequence listing, while the others were. The substituting sequence listing submitted herewith corrects this defect. As the Examiner will appreciate, the previous sequence listing contained a clerical error in SEQ ID NO:5. Instead of having 33 nucleotides (the Examiner will note that the length of each of the sequences from SEQ ID NO:3-9, increases by one triplet), it had a length of 28 nucleotides. The 5 missing nucleotides at the 5' end were thus added. No new matter is introduced by the introduction of this particular species.

The Abstract was amended as requested by the Examiner to correct informalities.

The Specification was also amended to correct a number of irregularities in the spelling and/or hyphenation of words.

Objection to Claim 32

The Examiner objected to Claim 32, indicating that Claim 32 did not reflect a change in SEQ ID NOs effected in a previous amendment. Claim 32 has been amended as suggested by the Examiner to recite SEQ ID NO: 18, thereby obviating this objection.

Rejections under 35 U.S.C.§112, first and second paragraphs

Claims 1-12, and 31-32 have been rejected under 35 U.S.C.§112, first paragraph, for lack of written description. In essence, the Examiner considers that while the instant Specification provides adequate written description for SEQ ID NO:18, it fails to adequately describe other nucleic acid sequences which may be encompassed by PAB II gene. In fact, the Examiner is of the opinion that "the disclosure does not teach any other specific sequence for PAB II besides that set forth in SEQ ID NO:18". Moreover, the Examiner states that the "disclosure fails to provide a clear description of unique characteristics or features which uniquely define a complete PAB II gene." Applicants respectfully traverse the objection as follows.

The gene in question, PAB II, is significantly conserved. For example, an example of the conservation between mouse (Mus musculus) and humans (Homo sapiens) for the gene is shown in Exhibit C, which shows that the polymorphic repeat described herein is 100% identical between human and mouse. Thus, one of ordinary skill in the art would be able to identify what is encompassed by a human PAB II as recited in the claims, as one would be able to identify exons and introns and/or intervening sequences in the human gene, particularly in view of its similarity to other non-human PAB II genes.

Furthermore, the present invention provides "the first description of short trinucleotide-repeat expansions causing a human disease" (see, e.g., page 8, line 27 of the present application). In addition, the present invention shows that "the PABP2 (GCG)7 allele is the first example of a relatively frequent allele which can act as a modifier of a dominant phenotype or as a recessive mutation" (see, e.g., instant invention page 8, line 30). The present invention teaches numerous polymorphic variants which are shown to be associated to different levels with disease. The

invention also describes novel distinguishing features of the sequences of the present invention (for example, these trinucleotide repeats had never been associated with human disease, they can modulate the severity of the disease). It is thus respectfully submitted that the polymorphic GCG repeats as defined in the pending claim, together with the demonstration that the length thereof is associated with a disease or non-disease phenotype (or the severity of the phenotypes or of the disease), meet the written description provision. In view of the above and foregoing the Applicants respectfully request that the Examiner withdraws his rejection of claims 1-12, and 31-32 for lack of written description.

The Examiner has also rejected claims 1-17, and 31-32 under 35 U.S.C.§112, first paragraph, for lack of enablement. The Examiner alleges that "while being enabling for an isolated human PAB II gene comprising a polymorphic repeat which is associated with oculopharyngeal muscular distrophy (OPMD) disease...does not reasonably provide enablement for sequences or methods which are indicative of protein accumulation in a cell nucleus, swallowing difficulty or ptosis" (emphasis in original). The Examiner states that "the instant Specification and the art teaches that patients with OPMD have the symptoms of protein accumulation in a cell nucleus, swallowing difficulty and ptosis, however the instant Specification fails to provide the nexus between patients with OPMD and patients with other disease that have one or more of the instantly claimed symptoms." As an example, the Examiner alleges that "difficulty in swallowing and ptosis are very general and common symtoms associated with many diseases with a diverse known etiology" (i.e. strep throat).

Applicants respectfully submit that in view of the combination of the recitation of the variants of the polymorphic GCG repeat in the human PAB II gene, and of the association of these variants with OPMD, in the pending claims, that the sequences and methods claims are enabled. With the aim at expediting the prosecution of the application, it should be noted that the language regarding specific symptoms has been deleted from Claims 1, 9 and 31. Furthermore, Claim 13 has been amended so that it now relates to a method for the diagnosis or prognosis of OPMD (thereby inserting the recitation of allowable claim 18 into claim 13). New claim 37, recites "associated with a phenotype of OPMD...". For the record, Applicants state that these

amendments should not be construed as an admission that claims 1, 9, 13, 31, as formerly written were non-enabled. Applicants reserve the right to prosecute such claims in further applications.

Claims 5, 6 and 9-12 have been rejected under 35 U.S.C.§112, second paragraph, as being indefinite. In view of the amendment to claim 5, which now recites "in said human patient" as suggested by the Examiner, the rejection of claims 5 and 6 has been rendered moot.

Claim 9 has been amended to indicate that the nucleic acid sequence encodes a human PAB II gene, and to recite the sequence of the GCG repeat. It is respectfully submitted that claim 9 clearly and distinctly set forth the metes and bounds of the particular sequences encompassed thereby.

In view of the above and foregoing, Applicants respectfully request that the Examiner withdraw the rejection of claims 1, 3-9, 11-17, and 31-32.

Rejections under 35 U.S.C.§102(b)

The Examiner has rejected claim 9, as allegedly being anticipated by Akarsu *et al.*, 1996. The Examiner is of the opinion that the GCG repeat recited in claim 9, is taught by Akarsu. More particularly, the Examiner states that "though this disease does not share the same symptoms as OPMD, the GCG repeat is nine repeats long and would meet the limitations of a GCG repeat associated with OPMD".

In order for a reference to anticipate claims, the reference must teach every aspect of the claimed invention either explicitly or impliedly (see M.P.E.P. § 2131). Akarsu *et al.* describe a repeat in the HOXD13 gene, which is associated with synpolydactyly. The amendment of Claim 9, which now recites the sequence of the polymorphic GCG sequence and specifies that it is in the human PAB II gene; therefore, Akarsu *et al.* do not teach every aspect of the claimed invention, and this rejection is believed to have been overcome.

Nevertheless, a comparison of the sequence of Akarsu and that of the GCG repeats of the present invention is shown hereinbelow to clearly demonstrate that the sequence of the former do not anticipate the latter.

GCG repeats: atg $(gcg)_{6+n}$ gca

HOXD13: cgg $(gcg)_4$ gca $(gcg)_2$ gct $(gcg)_3$ gca gcc gca gcc

GCG repeats: atg $(gcg)_4$ gcg $(gcg)_2$ gcg $(gcg)_3$ gca(when n=5)

The sequence of HOXD13, is clearly different from that of the GCG repeat of the present invention (underlined triplets indicate differences between the cited sequence and those of the present invention; e.g. "atg" vs "ctg"; "gcg" vs "gca"...).

In view of the above and foregoing, Akarsu *et al.* do not teach a GCG repeat as set forth in Claim 9. Therefore, Akarsu *et al.* do not teach every aspect of the claimed invention, so the invention is not anticipated by the teachngs of Akarsu *et al.* Withdrawal of the rejection of claim 9, under 35 U.S.C.§102(b) is respectfully solicited.

CONCLUSION

The rejections of claims 1, 3-9, 11-17, 31-32, and 37-39 have been overcome by the present remarks and by the amendments to the claims. From the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order, and such action is earnestly solicited.

If the Examiner believes that a telephone conversation would expedite prosecution of the application, the Examiner is invited to contact Elizabeth W. Mata at (915) 845-3558. If Elizabeth W. Mata cannot be reached, the Examiner is invited to contact David E. Brook at (978) 341-0036.

Respectfully submitted,

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Dated: 9c 1/8/02

MARKED UP VERSION OF AMENDMENTS

Specification Amendments Under 37 C.F.R. § 1.121(b)(1)(iii)

Please replace the paragraphs in the Specification, claims and Abstract as explained below with the corresponding paragraphs marked up by way of bracketing and underlining to show the changes relative to the previous version of the paragraph.

At page 1, line 14, through page 2, line 5 replace the paragraph with the following:

--Autosomal dominant oculopharyngeal muscular [dys-rophy]dystrophy (OPMD) is an adult-onset disease with a world-wide distribution. It usually presents itself in the sixth decade with progressive swallowing difficulties ([dys-phagia]dysphagia), eye lid drooping (ptosis) and proximal limb weakness. Unique nuclear filament inclusions in skeletal muscle fibers are its pathological hallmark (Tome, F.M.S. & Fardeau, Acta Neuropath. 49, 85-87 (1980)). Using the full power of linkage analysis in eleven French Canadian families, the oculopharyngeal muscular dystrophy gene was fine mapped on human chromosome 14 (Brais et al., 1997, Neuromuscular Disorders 7 (Suppl.1):S70-74). A region of .75 cM was thereby identified as a region containing the potential and unknown OMPD gene (Brais et al., 1997, *supra*). Unfortunately, the OMPD gene has yet to be isolated and its nucleic acid or protein sequence have yet to be [cribbed] described.--

At page 2, lines 13-22, replace the paragraph with the following:

--Herein, the poly(A) binding protein II (PAB II) gene was isolated from a 217 kb candidate interval in chromosome 14q11.A (GCG)6 repeat encoding a polyalanine tract located at the N-terminus of the protein was expanded to (GCG)8-13 in the 144 OPMD families screened. More severe [pheno-types] phenotypes were observed in compound heterozygotes for the (GCG)9 mutation and a (GCG)7 allele found in 2% of the population, whereas homozygosity for the (GCG)7 allele leads to autosomal recessive OPMD. Thus the (GCG)7 allele is an example of a polymorphism which can act as either a modifier of a dominant phenotype or as a recessive mutation. Pathological expansions of the polyalanine tract may cause mutated PAB II oligomers to accumulate as filament inclusions in nuclei.--

At page 2, lines 23-25, replace the paragraph with the following:

--In accordance with the present invention there is provided a human PAB II gene containing a transcribed polymorphic GCG repeat, which comprises a sequence as set forth in Fig. 4, which includes introns and [flank-ing] flanking genomic sequence.--

At page 3, lines 3-10, replace the paragraphs with the following:

--In accordance with the present invention there is also provided a method for the diagnosis of a [dis-ease] disease associated with protein accumulation in the nucleus, which comprises the steps of:

a) obtaining a nucleic acid sample of said patient; and
b) determining allelic variants of a GCG repeat of the human PAB II gene; [thereby] whereby long allelic variants are indicative of a disease related with protein accumulation in the nucleus, such as polyalanine accumulation and oculopharyngeal muscular dystrophy.--

At page 3, lines 17-26, replace the paragraphs with the following:

--In accordance with the present invention there is also provided a method for the screening of [thera-peutic] therapeutic agents for the prevention and/or treatment of oculopharyngeal muscular dystrophy, which comprises the steps of:

a) administering the therapeutic agents to the non-human animal of the present invention or oculopharyngeal muscular dystrophy patients; and
b) evaluating the prevention and/or treatment of development of oculopharyngeal muscular [dystro-phy]dystrophy in this animal (such as a mammal) or in patients.

In accordance with the present invention there is also provided a method to identify genes[-], products thereof, or part thereof, which interact with a biochemical pathway affected by the PAB II gene, which comprises the steps of:--

At page 4, lines 15-21, replace the paragraph with the following:

--In order to identify the gene mutated in OPMD, a 350 kb cosmid contig was constructed between flanking markers D14S990 and D14S1457 (Fig. 1A). Positions of the PAB II-selected

cDNA clones were determined in relation to the EcoRI restriction map and the Genealogy-based Estimate of Historical Meiosis (GEHM)-derived candidate interval (Rommens, J.M. et al., in Proceedings of the third international workshop on the identification of [tran-scribed] transcribed sequences (eds. Hochgeschwender, U. & Gardiner, K.) 65-79 (Plenum, New York, 1994)).--

At page 4, line 24, carrying over to page 5, line 9, replace the paragraph with the following:

--Twenty-five cDNAs were isolated by cDNA [selec-tion] selection from the candidate interval (Rommens, J.M. et al., in Proceedings of the third international workshop on the identification of transcribed sequences (eds. Hochgeschwender, U. & Gardiner, K.; 65-79; Plenum, New York, 1994). Three of these hybridized to a common 20 kb EcoRI restriction fragment and showed high sequence homology to the bovine poly(A) binding protein II gene (bPAB II) (Fig. 1A). The PAB II gene appeared to be a good candidate for OPMD because it mapped to the genetically defined 0.26 cM candidate interval in 14q11 (Fig. 1A), its mRNA showed a high level of expression in skeletal muscle, and the PAB II protein is [exclu-sively] exclusively localized to the nucleus (Krause, S. et al., Exp. Cell Res. 214, 75-82 (1994)) where it acts as a factor in mRNA polyadenylation (Whale, E., Cell 66, 759-768 (1991); Whale, E. et al., J. Biol. Chem. 268, 2937-2945 (1993); Bienroth, S. et al., EMBO J. 12, 585-594 (1993)).--

At page 5, lines 10-15, replace the paragraph with the following:

--A 8 kb HindIII genomic fragment containing the PAB II gene was subcloned and sequenced (6002 bp; GenBank: AF026029)(Nemeth, A. et al., Nucleic Acids Res. 23, 4034-4041 (1995)) (Fig. 1B). Genomic structure of the PAB II gene, and position of the OPMD (GCG)n expansions. Exons are numbered. Introns 1 and 6 are variably present in 60% of cDNA clones. ORF, open [read-ing] reading frame; cen, centromere and tel, telomere.--

At page 5, line 16, carrying over to page 6, line 2, replace the paragraph with the following:

--The coding sequence was based on the previously published bovine sequence (GenBank: X89969) and the sequence of 31 human cDNAs and ESTs. The gene is [comùposed] composed of 7 exons and is transcribed in the cen-qter orientation (Fig. 1B). Multiple splice variants are found in ESTs and on Northern blots (Nemeth, A. et al., Nucleic Acids Res. 23, 4034-4041 (1995)). In

particular, introns 1 and 6 are present in more than 60% of clones (Fig. 1B)(Nemeth, A. et al., Nucleic Acids Res. 23, 4034-4041 (1995)). The coding and protein sequences are highly conserved between human, bovine and mouse (GenBank: U93050). 93% of the PAB II sequence was [read-ily] readily amenable to RT-PCR- or genomic-SSCP screening. No mutations were uncovered using both techniques. [How-ever] However, a 400 bp region of exon 1 containing the start codon could not be readily amplified. This region is 80% GC rich. It includes a (GCG)6 repeat which codes for the first six alanines of a homopolymeric stretch of 10 (Fig. 2G). Nucleotide sequence of the mutated region of PAB II as well as the amino acid sequences of the N-terminus polyalanine stretch and position of the OPMD alanine insertions is also shown in Fig. 2.--

At page 6, lines 10-16, replace the paragraph with the following:

--Sequencing of these fragments revealed that the increased sizes were due to expansions of the GCG repeat (Fig. 2G). Fig. 2F shows the sequence of the (GCG)9 French Canadian expansion in a heterozygous [par-ent] parent and his homozygous child. Partial sequence of exon 1 in a normal (GCG)6 control (N), a heterozygote (ht.) and a homozygote (hm.) for the (GCG)9-repeat mutation. The number of families sharing the different (GCG)n-repeats expansions is shown in Table 1. --

At page 7, lines 15-21, replace the paragraphs with the following:

--The (GCG)9 expansion shared by 70 French [Cana-dian] Canadian families is the most frequent mutation we observed (Table 1) The (GCG)9 expansion is quite stable, with a single doubling observed in family F151 in an estimated 598 French Canadian meioses (Fig. 2C). The doubling of the French Canadian (GCG)9 expansion is demonstrated in Family F151.

This contrasts with the unstable nature of [preùviously] previously described disease-causing [triplet-repeats] triplet repeats (Rosenberg, R.N., New Eng. J. Med. 335, 1222-1224 (1996)).--

At page 7, line 22, carrying over to page 8, line 12, replace the paragraph with the following:

--Genotyping of all the participants in the [clini-cal] clinical study of French Canadian OPMD provided molecular insights into the clinical variability observed in this condition. The genotypes for both copies of the PAB II mutated region were added to an anonymous version of this

clinical database of 176 (GCG)9 mutation carriers (Brais, B. et al., Hum. Mol. Genet. 4, 429-434 (1995)). Severity of the phenotype can be assessed by the [swal-lowing time] swallowing (st) in seconds taken to drink 80 cc of ice-cold water (Brais, B. et al., Hum. Mol. Genet. 4, 429-434 (1995); Bouchard, J.-P. et al., Can. J. Neurol. Sci. 19, 296-297 (1992)).The late onset and [progres-sive] progressive nature of the muscular dystrophy is clearly [illus-trated] illustrated in heterozygous carriers of the (GCG)9 mutation (bold curve in Fig. 3) when compared to the average st of control (GCG)6 homozygous participants(n=76, thinner line in Fig. 3). The bold curve represents the average OPMD st for carriers of only one copy of the (GCG)9 mutation (n=169), while the thinner line corresponds to the average st for (GCG)6 homozygous normal [con-trols] controls (n=76).The black dot corresponds to the st value for individual VIII. Roman numerals refer to individual cases shown in Figs. 2B, 2D and discussed in the text. The genotype of a homozygous (GCG)9 patient and her parents is shown in Fig. 2B. Independent segregation of the (GCG)7 allele is also shown. Of note, case V has a more severe OPMD phenotype (Fig. 2D).--

At page 8, lines 13-26, replace the paragraph with the following:

--Two groups of genotypically distinct OPMD cases have more severe swallowing difficulties. Individuals I, II, and III have an early-onset disease and are homozygous for the (GCG)9 expansion ($P < 10\text{-}5$) (Figs. 2B, F). Cases IV, V, VI and VII have more severe phenotypes and are compound heterozygotes for the (GCG)9 mutation and the (GCG)7 polymorphism ($P < 10\text{-}5$). In Fig. 2D the independent segregation of the two alleles is shown. Case V, who inherited the French Canadian (GCG)9 mutation and the (GCG)7 polymorphism, is more symptomatic than his brother VIII who carries the (GCG)9 mutation and a normal (GCG)6 allele (Figs. 2D and 3). The (GCG)7 polymorphism thus appears to be a modifier of severity of dominant OPMD. [Further-more]Furthermore, the (GCG)7 allele can act as a recessive [mutaùtion] mutation. This was documented in the French patient IX who inherited two copies of the (GCG)7 polymorphism and has a late-onset autosomal recessive form of OPMD (Fig. 2E). Case IX, who has a recessive form of OPMD, is shown to have inherited two copies of the (GCG)7 polymorphism.--

At page 8, line 27, carryiong over to page 9, line 18, replace the paragraph with the following:

--This is the first description of short [trinu-cleotide] trinucleotide repeat expansions causing a human disease. The addition of only two GCG repeats is sufficient to cause dominant OPMD. OPMD expansions do not share the [cardi-nal] cardinal features of "dynamic mutations". The GCG expansions are not only short they are also meiotically quite [sta-ble] stable. Furthermore, there is a clear cut-off between the normal and abnormal alleles, a single GCG expansion causing a recessive phenotype. The PAB II (GCG)7 allele is the first example of a relatively frequent allele which can act as either a modifier of a dominant [pheno-type] phenotype or as a recessive mutation. This dosage effect is reminiscent of the one observed in a homozygote for two dominant synpolydactyly mutations. In this case, the patient had more severe deformities because she [inher-ited] inherited two duplications causing an expansion in the polyalanine tract of the HOXD13 protein (Akarsu, A.N. et al., Hum. Mol. Genet. 5, 945-952 (1996)). A [duplica-tion] duplication causing a similar polyalanine expansion in the [a] α subunit 1 gene of the core-binding transcription factor (CBF(1) has also been found to cause dominant cleido-cranial dysplasia (Mundlos, S. et al., Cell 89, 773-779 (1997)). The mutations in these two rare diseases are not [triplet-repeats] triplet repeats. The are duplications of "cryptic repeats" composed of mixed synonymous codons and are thought to result from unequal crossing over (Warren, S.T., Science 275, 408-409 (1997)). In the case of OPMD, slippage during replication causing a reiteration of the GCG codon is a more likely mechanism (Wells, D.R., J. Biol. Chem. 271, 2875-2878 (1996)).--

At page 9, line 19, carrying over to page 10, line 17, replace the paragraph with the following:

--Different observations converge to suggest that a gain of function of PAB II may cause the accumulation of nuclear filaments observed in OPMD (Tome, F.M.S. & Fardeau, Acta Neuropath. 49, 85-87 (1980)). PAB II is found mostly in dimeric and oligomeric forms (Nemeth, A. et al., Nucleic Acids Res. 23, 4034-4041 (1995)). It is possible that the polyalanine tract plays a role in polymerization. Polyalanine stretches have been found in many other nuclear proteins such as the HOX [pro-teins] proteins, but their function is still unknown (Davies, S.W. et al., Cell 90, 537-548 (1997)). Alanine is a highly hydrophobic amino acid present in the cores of proteins. In dragline spider silk, polyalanine stretches are thought to form [B]β-sheet structures [impor-tant] important in ensuring the fibers' strength (Simmons, A.H. et al., Science 271, 84-87 (1996)). Polyalanine

oligomers have also been shown to be extremely resistant to chemical denaturation and enzymatic degradation (Forood, B. et al., Bioch. and Biophy. Res. Com. 211, 7-13 (1995)). One can speculate that PAB II oligomers comprised of a sufficient number of mutated molecules might accumulate in the nuclei by forming undegradable polyalanine rich macromolecules. The rate of the [accuùmulation] accumulation would then depend on the ratio of mutated to non-mutated protein. The more severe phenotypes observed in homozygotes for the (GCG)9 mutations and compound heterozygotes for the (GCG)9 mutation and (GCG)7 allele may correspond to the fact that in these cases PAB II oligomers are composed only of mutated proteins. The ensuing faster filament accumulation could cause accelerated cell death. The recent [descrip-tion] description of nuclear filament inclusions in Huntington's disease, raises the possibility that "nuclear toxicity" caused by the accumulation of mutated homopolymeric domains is involved in the molecular pathophysiology of other [triplet-repeats] triplet repeats diseases (Davies, S.W. et al., Cell 90, 537-548 (1997); Scherzinger, E. et al., Cell 90, 549-558 (1997); DiFiglia, M. et al., Science 277, 1990-1993 (1997)). Future immunocytochemical and expression studies will be able to test this [patho-physiological] pathophysiological hypothesis and provide some insight into why certain muscle groups are more affected while all tissues express PAB II.--

At page 11, replace the paragtaph at lines 2-7 with the following:

--Three cDNA clones corresponding to PAB II were sequenced (Sequenase, USB). Clones were verified to map to cosmids by [South-ern] Southern hybridization. The 8 kb HindIII restriction [frag-ment] fragment was subcloned from cosmid 166G8 into pBluescriptII (SK) (Stratagene). The clone was sequenced using [prim-ers] primers derived from the bPABII gene and human EST sequences. Sequencing of the PAB II introns was done by primer walking.--

At page 11, line 9, carrying over to page 12, line 2, replace the paragraph with the following:

--All cases were diagnosed as having OPMD on clinical grounds (Brais, B. et al., Hum. Mol. Genet. 4, 429-434 (1995)). [RT-PCR-] RT-PCR and genomic SSCP analyses were done using [stan-dard] standard protocols (Lafrenière, R.G. et al., Nat. Genet. 15, 298-302 (1997)). The primers used to amplify the PAB II mutated region were: 5'-CGCAGTGCCCCGCCTTAGA-3' (SEQ ID NO:4) and 5'-ACAAGATGGCGCCGCCGCCCCGGC-3' (SEQ ID NO:5). PCR reactions

were performed in a total volume of 15 µl containing: 40 ng of genomic DNA; 1.5 µg of BSA; 1 µM of each primer; 250 µM dCTP and dTTP; 25 µM dATP; 125 µM of dGTP and 125 µM of 7-deaza-dGTP (Pharmacia); 7.5% DMSO; 3.75 µCi[^{35}S]dATP, 1.5 unit of Taq DNA polymerase and 1.5 mM MgCl2 (Perkin Elmer). For non-radioactive PCR reactions the [^{35}S]dATP was replaced by 225 µM of dATP. The amplification procedure consisted of an initial [denatuùration] denaturation step at 95°C for five minutes, followed by 35 cycles of denaturation at 95°C for 15 s, annealing at 70°C for 30 s, elongation at 74°C for 30 s and a final elongation at 74°C for 7 min. Samples were loaded on 5% polyacrylamide [denatur-ing] denaturing gels. Following electrophoresis, gels were dried and autoradiographs were obtained. Sizes of the inserts were determined by comparing to a standard M13 sequence (Sequenase™, USB). Fragments used for sequencing were gel-purified. Sequencing of the mutated fragment using the Amplicycle kit™ (Perkin Elmer) was done with the 5'-CGCAGTGCCCCGCCTTAGAGGTG-3' (SEQ ID NO:6) primer at an elongation temperature of 68°C.--

At page 12, lines 4-15, replace paragraph with the following:

--The meiotic stability of the (GCG)9-repeat was estimated based on a large French Canadian OPMD cohort. It had been previously established that a single ancestral OPMD carrier [chro-mosome] chromosome was introduced in the French Canadian population by three sisters in 1648. Seventy of the seventy one French Canadian OPMD families tested to date segregate a (GCG)9 expansion. However, in family F151, the affected brother and sister, despite sharing the French Canadian ancestral haplotype, carry a (GCG)12 expansion, twice the size of the ancestral (GCG)9 mutation (Fig. 2C). In this founder effect study, it is estimated that 450 (304-594) historical meioses shaped the 123 OPMD cases belonging to 42 of the 71 enrolled families. The screening of the full set of participants allowed an identification of another 148 (GCG)9 carrier chromosomes. Therefore, it is estimated that a single mutation of the (GCG)9 expansion has occurred in 598 (452-742) meioses.--

At page 13, lines 3-9, replace the paragraph with the following:

--While the invention has been described in [con-nection] connection with specific embodiments thereof, it will be understood that it is capable of further modifications and this application is intended to cover any [vari-ations] variations, uses, or adaptations of the invention

[follow-ing] following, in general, the principles of the invention and including such departures from the present disclosure as come within known or customary practice within the art to which the invention pertains and as may be applied to the essential features hereinbefore set forth, and as follows in the scope of the appended claims.--

Claim amendments

1. (Amended) An isolated human PAB II gene comprising a polymorphic GCG repeat in exon I thereof, wherein said polymorphic GCG repeat has the sequence

$$ATG\ (GCG)_{6+n}\ GCA,$$

with n being selected from 1 to 7 and wherein an allelic variant of said GCG repeat is indicative of a disease [associated with protein accumulation in a cell nucleus, swallowing difficulty, and/or ptosis] in a human patient.

3. (Amended) The gene of claim [2]1, wherein n is selected from 2 to 7, and wherein said allelic variant is associated with an increased severity of the disease.

5. (Amended) The gene of claim [2]1, wherein in said human patient, a first allele of said GCG repeat has an n which is equal to 1.

9. (Amended) A nucleic acid sequence comprising a polymorphic GCG repeat of exon I of [a] the human PAB II gene, wherein said polymorphic GCG repeat has the sequence

$$ATG\ (GCG)_{6+n}\ GCA,$$

with n being selected from 1 to 7 and wherein an allelic variant of said polymorphic GCG repeat in a patient's human PAB II gene is indicative of a disease [associated with protein accumulation in a cell nucleus, swallowing difficulty, and/or ptosis] in said human patient.

11. (Amended) The nucleic acid sequence of claim [10] 9, wherein n is selected from 2 to 7, and wherein said allelic variant is associated with an increased severity of said disease.

13. (Amended) A method for the diagnosis or prognosis of oculopharyngeal muscular dystrophy (OPMD) a disease associated with protein accumulation in a cell nucleus, and/or swallowing difficulty and/or ptosis in a human patient, which comprises:

a) obtaining a nucleic acid sample of said patient; and

b) determining allelic variants of a GCG repeat in exon I of the PAB II gene, said GCG repeat having the sequence

$$ATG\ (GCG)_{6+n}\ GCA,$$

wherein n is selected from 0 to 7, and

whereby at least one [allele] of the two alleles of said GCG repeat [having] has an n equal to 1 to 7, and is indicative of [a disease related with said protein accumulation in said nucleus, and/or a swallowing difficulty and/or ptosis in said patient] OPMD.

16. (Amended) The method of claim 13, wherein [a] said first allele of said GCG repeat has an n which is equal to 1.

17. (Amended) The method of claim 16, wherein [a] said second allele of said GCG repeat has an n selected from 2 to 7, and wherein said first allele is a modulator of the severity of the phenotype associated with said second allele.

31. (Amended) An isolated human PAB II gene comprising a polymorphic GCG repeat in exon I thereof, wherein said repeat has the sequence $ATG\ (GCG)_{6+n}\ GCA$, wherein n is 0, and wherein said sequence is indicative of a non-disease phenotype [associated with protein accumulation in a cell nucleus, swallowing difficulty, and/or ptosis] in a human patient.

32. (Amended) The human PAB II gene of claim 31, wherein said gene is as set forth in SEQ ID NO:[3]18.

Please add the following new claims:

37. An isolated PAB II nucleic acid sequence comprising a polymorphic GCG repeat having the sequence

$$ATG\ (GCG)_{6+n}\ GCA,$$

wherein n is selected from the group consisting of:

a) n=0, wherein said nucleic acid sequence is associated with a non-disease phenotype; and

b) n is selected from 1 to 7, wherein said nucleic acid sequence is associated with a phenotype of oculopharyngeal muscular distrophy, selected from at least one of protein accumulation in a cell nucleus, swallowing difficulty, and ptosis.

38. The isolated nucleic acid sequence of claim 37, wherein n=0, and wherein said sequence comprises the sequence as set forth in SEQ ID NO:18.

39. The isolated nucleic acid sequence of claim 37, wherein n=0, and wherein said sequence comprises the sequence as set forth in SEQ ID NO:1.

Abstract amendments

--SHORT GCG EXPANSIONS IN THE PAB II GENE FOR OCULO-PHARYNGEAL MUSCULAR DYSTROPHY AND DIAGNOSTIC THEREOF

ABSTRACT OF THE DISCLOSURE

The present invention relates to a human PAB II gene containing transcribed polymorphic GCG repeat, which comprises a sequence as set forth in SEQ ID NO:[3]18, which includes introns and flanking genomic sequence. [The allelic] Allelic variants of GCG repeat of the human PAB II gene are associated with a disease related with protein accumulation in the nucleus, such as polyalanine [accumula-tion] accumulation, or [a disease related] with swallowing difficulties, such as oculopharyngeal muscular dystrophy. The [pres-ent] present invention also relates to a method for the [diagno-sis] diagnosis of a disease associated with protein accumulation in the nucleus, which comprises the steps of: a) obtaining a nucleic acid sample of [said] a patient; and b) determining allelic variants of GCG repeat of the PAB II gene [of claim 1], and wherein long allelic variants are indicative of a [dis-ease] disease related with protein accumulation in the nucleus.--